

**Usefulness of white blood cell count in the diagnosis of infection:
comparison between young and geriatric hospitalized groups.**

20/02/2019

Protocol Clinical Trial

Abstract

Title of the project

Usefulness of white blood cell count (WBCC) during infection: a comparison between hospitalized geriatric and young groups.

Objective of the study

In the general population, increased WBCC and neutrophil count are widely used as markers for infection during inflammatory states ¹. However, 32% of geriatric patients with an infection do not develop an increase in WBCC ². The hypothesis is that with inflammation, geriatric patients have a misadapted response of the immune system (IS) ³.

Our recent retrospective study ⁴ has shown that total and differential WBCC were not correlated with infection in a geriatric hospitalized population. Therefore, WBCC does not seem to be a reliable marker for infection in geriatric hospitalized patients. The neutrophil/lymphocyte ratio, and CRP, seem to be better markers.

We propose to investigate this hypothesis prospectively and assess the role of aging and chronic diseases (such as cardiovascular diseases (CVD) and risk factors (CVRF) ⁵, cytomegalovirus (CMV) infection ⁶, periodontitis ⁷, onychomycosis ⁸) in this process and assess the role of a geriatric assessment.

To assess the usefulness of WBCC in the diagnosis of infection in geriatric patients and to address the contribution of ongoing chronic co-morbidities and age to WBCC-kinetics during an acute inflammatory syndrome, we will compare young and geriatric hospitalized patients with an inflammatory syndrome with and without infection.

Investigator(s)

Hanne Maes (student master geneeskunde VUB) = principal investigator
Prof. Dr. Nathalie Compté (geriatrics UZ Brussel) = promotor
Prof. Dr. Bert Bravenboer (geriatrics UZ Brussel) = head of department
Prof. Dr. Tony Mets

Sponsor

No sponsor

Departments/laboratories involved in the study

UZ Brussels geriatrics department
UZ Brussels emergency department
UZ Brussels rheumatology department, pneumology department, endocrinology department
UZ Brussels central laboratory

Introduction

In the general population, increased white blood cell count (WBCC) and neutrophils are widely used as markers for bacterial infection during inflammatory states ¹. However, 32% of geriatric patients with infection do not get an increase in WBCC during infection ². The hypothesis is that with inflammation, geriatric patients get a misadapted response of the immune system (IS) ³.

Ageing is associated with immune dysfunction. Older people have a decreased phagocytosis and chemotaxis by neutrophils ⁹, a decreased T-cell activation by dendritic cells, a decreased response of the innate immune system during Toll-like receptor stimulation ¹⁰, a decrease number of naive B- and T-cells ¹¹, an increase number of memory B- and T-cells ¹², increased presence of monoclonal Ab (MGUS) ¹³, and an increase in exhausted, senescent T-cells ¹⁴. This remodeling of the immune system could lead to a higher prevalence of infection, auto-immune diseases, and cancer in geriatric patients ¹². Ageing is also associated with low-grade inflammation: a process called inflammaging ¹⁵. The origin of inflammaging is multifactorial and is associated with cardiovascular risk factors (CVRF) and diseases (CVD) ⁵, chronic cytomegalovirus (CMV) infection ⁶, periodontitis ⁷, onychomycosis ⁸, microbiota changes ¹⁶, increased intestinal permeability ¹⁷ and senescent cells ¹⁴.

Inflammaging is associated with the geriatric syndrome and mortality but also with centenarians and longevity ¹⁸. The inflammaging process seems to be a result of an adaptation to encountered stressors during life: the immunobiography of the individual. The immunobiography of the patients could influence the function of the IS leading to a well-

adapted response of the IS such as in centenarians, or to a mis-adapted response of the IS such as in geriatric patients ³. Consequently, the WBCC response in geriatric patients during infection could be well or mis- adapted, depending on the immunobiography. ¹⁴

An inflammatory state is characterized by an acute phase response with increased CRP, in both acute and chronic inflammation ¹⁹. A rise of CRP can point to an acute infection but also to an inflammatory disease such as CV diseases, autoimmune diseases, thrombosis, stroke, pulmonary embolism, ...

Our recent retrospective study from 2018 has shown that there was no correlation between total and differential WBCC and infection in a geriatric hospitalized population ⁴. Therefore, the WBCC does not seem to be a reliable marker for infection in geriatric hospitalized patients. The neutrophil/lymphocyte ratio and CRP appeared to be better markers.

The aim of the present study is to assess the usefulness of WBCC in the diagnosis of infection in geriatric patients and to address the contribution of ongoing chronic co-morbidities and age to WBCC kinetics during an acute inflammatory syndrome. We shall compare young and geriatric hospitalized patients with an inflammatory syndrome with and without infection.

Study design

Observational prospective study

The subjects

Number of subjects

200 subjects:

Average value CRP: group 1: 55; group 2: 84

Average standard deviation: 70.52

Power 80%: 158 deelnemers

Power 90%: 202 deelnemers

alpha = 0.05

2-sample T-test.

Inclusion criteria

Acute inflammation is defined as a CRP ≥ 10 mg/l. We will include 2 groups of participants:

=> A) A group with an inflammatory syndrome and infection; infection being defined as:

1. Viral infection confirmed by nasopharynx swab for: influenza, RSV, parainfluenza, rhinoviruses, coronaviruses.

2. Bacterial infection confirmed with positive blood culture, positive articular puncture, positive expectorations, pneumonia on chest radiograph, or infection documented by abdominal imagery (CT or echo), a positive urine culture with a confirmed pyelonephritis with a renal echography or a DMSA scintigraphy or specific clinical symptoms for pyelonephritis and positive hemoculture. A positive urine culture alone is not considered as urine infection because of the high prevalence of asymptomatic bacteriuria in geriatric patients.

=> B) A group with inflammatory syndrome and inflammatory diseases without infection: defined as:

1. Confirmed pulmonary embolism (PE) by CT or ventilation-perfusion scintigraphy
2. Microcrystalline arthritis diagnosed by articular puncture
3. Crush syndrome or rhabdomyolyses defined by history of a fall and raised creatine kinase in blood sample.

Exclusion criteria

Immunosuppressive therapy (NSAIDs, corticosteroids, chemotherapy, immunotherapy), active cancer, antibiotics before admission, hematological diseases

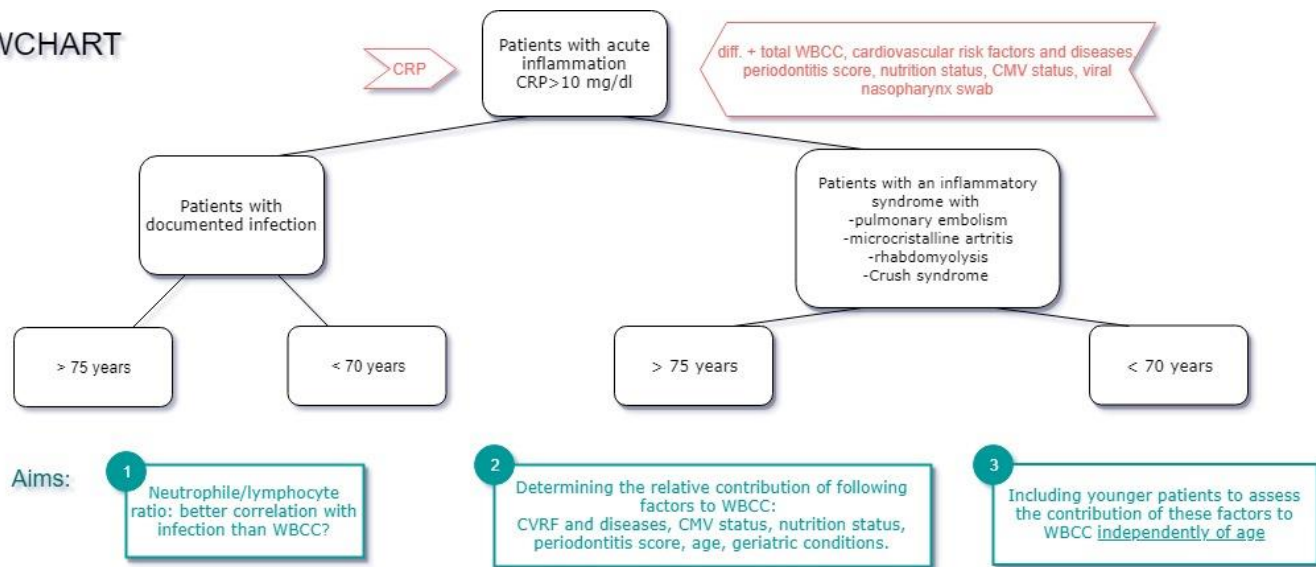
Replacement of subjects

None.

Restrictions and prohibitions for the subjects

None.

FLOWCHART



Procedures

A) Questionnaires:

taken at UZ Brussels

-Social: age, home, sex, marital status.

-Clinical: smoking and alcohol habits, streptococcus pneumoniae and influenza vaccination status, allergies, BMI, medical history, current treatment, reason for current hospitalization.

-Comprehensive geriatric assessment:

-CIRS-G (Cumulative Illness Rating Score): to quantify disease burden. It rates each organ system on a scale of 0 to 4, and differentiates older adults with the highest risk of and severity of infection, from those with lower infection risk.²⁰

-Katz scale (ADL: assessment of activities of daily living): It rates 6 tasks of daily living (bathing, dressing, toilet, transfer, continence and eating) on a scale from 1 to 4. A low score means absence of dependence, and a high score the maximum of dependence for the task.²¹

-MMSE (Mini Mental Status Examination): a 0-30 score of cognitive functions, <24/30 meaning cognitive function impairment.²² Patients with dementia: we will request approval to be included in the study to the family of the patients.

-MUST (Malnutrition Universal Screening Tool): to assess nutritional status. It divides patients into 3 groups: A low risk of malnutrition (score 0). A medium risk of malnutrition (score 1): then it is recommended to observe the patient for dietary intake. A high risk of malnutrition (score ≥ 2): treat the malnutrition.²³

-Questionnaire for periodontal health. The newly developed questionnaire produces a reliable assessment of the individual risk of periodontitis (total score) and the need for periodontal treatment as well as the differentiation between gingivitis and periodontitis.²⁴

-Grip strength: Inflammatory states in the elderly are also associated with a decrease in muscle strength and fatigue resistance, as seen at UZ Brussels by Bautmans et al. The reduced strength and fatigue resistance in geriatric patients with inflammation are significantly related with the concentration of circulating CRP levels.²⁵ In our study we will use the martin vigorimeter which is at our disposal at the geriatrics ward of UZ Brussels, to measure the patients' grip strength and muscle fatiguability and determine which factors seem to contribute to a decrease in muscle strength (CRP, CVD, CVR, infection, periodontitis, CMV status, onychomycosis, age). We will use the Martin vigorimeter (Elmed, Addison, IL) to assess grip strength and fatiguability. We will ask the patients to squeeze the rubber bulb of the vigorimeter as hard as possible in 3 consecutive attempts, to assess their grip strength. The highest score for each hand is recorded. Fatigue resistance will be assessed by asking the patient to squeeze the bulb of the vigorimeter as hard as possible and to maintain this pressure as long as possible; the time (seconds) until the pressure diminished to half of the maximal grip strength is recorded for each hand.^{25 26}

B) Collection of data from physical examination

C) Clinical evaluation of onychomycosis of the toenails: We will perform a clinical examination of the toenails. Following parameters are found to be significantly related to positive mycology results in onychomycosis patients⁸: scaling on one or both soles, white crumbly patches on the nail surface, and an abnormal colour of the nail.

D) Follow up of bacterial and viral culture analyses

Observational data from bacterial and viral samples during hospitalization :

1. Viral infection confirmed by nasopharynx swab for: influenza, RSV, parainfluenza, rhinoviruses, coronaviruses
2. Bacterial infection confirmed with positive blood culture, positive articular puncture, positive expectorations, pneumonia on chest radiograph, or infection documented by abdominal imagery (CT or echo), a positive urine culture with a confirmed pyelonephritis with a renal echography or a DMSA scintigraphy or specific clinical symptoms for pyelonephritis and positive hemoculture. A positive urine culture alone is not considered as urine infection because of the high prevalence of asymptomatic bacteriuria in geriatric patients.

E) Follow up of blood analyses:

Observational data from blood samples during hospitalization:

- Day 0 (at the emergency department): CRP, total and differential WBCC, renal function
- Day 1: at hospitalization, within 24h of admission

- Geriatric patients: CRP, total and differential WBCC, renal function, hepatic function (transaminases), albumin, prealbumin, protein profile and monoclonal protein, vitamin B12, folic acid, hemoglobin, hematocrit, TSH, CMV-serology.

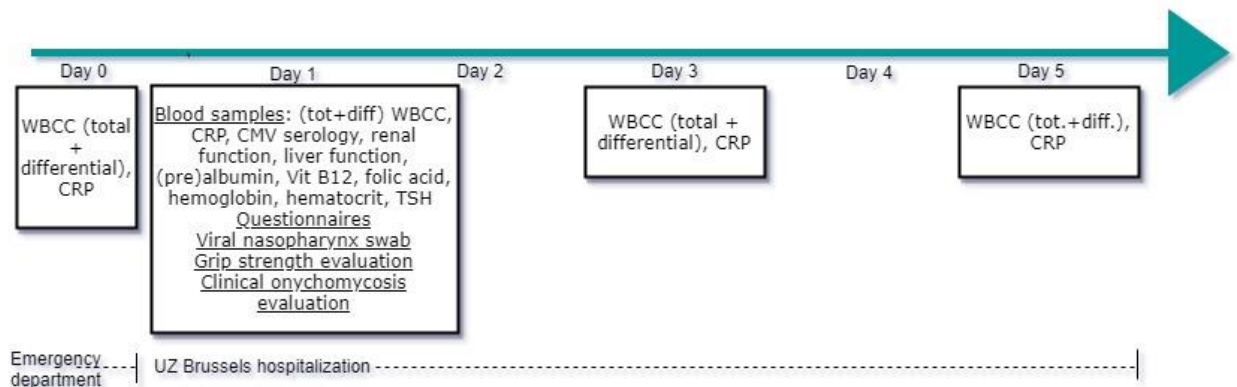
- Young patients: CRP, total and differential WBCC, renal function, albumin, vitamin B12, folic acid, TSH, CMV-serology.

-Day 3: CRP, total and differential WBCC.

-Day 5: CRP, total and differential WBCC.

Flowchart

TIMELINE



Questionnaires, blood samples: conducted by Hanne Maes. Supervising MD: Dr. Nathalie Compté, UZ Brussels.

Randomisation/blinding

Observational study, not applicable.

Prior and concomitant therapy

All medication can be continued during this study.

Study analysis

Statistical analysis

We will perform student t-tests or Mann-Whitney rank sum tests to compare geriatric/young patients with and without infection. To assess the contribution of age, comorbidities and geriatric syndrome in the kinetics of WBCC, we will perform univariate and multivariate analyses.

Quality control and quality assurance

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Publication policy

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